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Compensatory renal growth symposium: An introduction

The subject of compensatory renal hypertrophy and regeneration has received relatively little attention from nephrologists and renal physiologists. Perusal of the table of contents in any major kidney-oriented textbook reveals little or no space devoted to it. Symposia concerned principally with renal hormones or metabolism rarely mention a circulating renotropin and/or a system regulating compensatory renal hypertrophy and regeneration of damaged tissue.

Compensatory renal hypertrophy with hyperplasia is the enlargement and new formation of cells following loss of renal mass that cannot be replaced in situ. The most common example is the hypertrophy and hyperplasia of the remaining kidney tissue after surgical extirpation of one kidney (unilateral nephrectomy). Regeneration occurs when the original renal mass returns both anatomically and functionally via hyperplasia toward its original state following damage, such as seen in acute tubular necrosis. Obviously, both processes, hypertrophy and regeneration, could result from the same, overlapping, or even an entirely different mechanism. For simplicity, we will refer to both processes under the single term, compensatory renal growth (CRG).

The first major symposium devoted to CRG was held in Galveston, Texas, in 1968; the proceedings were published in a book entitled, *Compensatory Renal Hypertrophy* edited by Drs. W. W. Nowinski and R. J. Goss [1]. Eight years later, a conference concerned in part with biochemical and molecular responses to loss of renal mass was held in Lausanne, Switzerland. The proceedings of this meeting on Renal Adaptation to Nephron Loss were published originally in the *Yale Journal of Biology* [2] and later by the S. Karger Company, Switzerland [3]. Now, 6 years later, we have attempted to update the subject by gathering papers on various aspects of CRG written by experts in the field. Each paper has been arbitrarily placed in one of three general sections. The first section contains contributions principally concerned with the physiology and biochemistry of CRG. The second section includes those works pertaining to the existence of a renotropic factor(s) which specifically incites and/or regulates CRG. Perhaps, the greatest gains have been made in this area since the last symposium was held in Switzerland. The third section is devoted to two disorders that have been associated with CRG, namely hypertension and diabetes mellitus. Assuming that a renotropic factor exists, the additional biochemical and physiological influences of renotropin could be an area where future research may prove beneficial.

Biochemistry and physiology of CRG

To derive an extensive background concerning early history and the effects of diets and other environmental factors on DNA, RNA, and other aspects of biochemistry in CRG, one might start with the contributions in the first and second symposia [1–3] and other earlier writings [4, 5].

In brief, survival of the organism is dependent, to a great extent, on the ability of renal hypertrophy and/or hyperplasia to return viable renal tissue after excessive destruction of renal parenchyma. Following unilateral nephrectomy, an early increase in wet and dry renal mass is noted. Changes in bulk RNA may be seen by 24 hr, followed later by enhancement of protein and DNA synthesis (Fig. 1). Changes are also noted in mitotic activity, and polysomal composition [6]. Uptake of radioactive precursor into RNA are detectable early. Toback, Smith and Lowenstein [7] found increases in phospholipid synthesis (choline incorporation into lipids) within 5 min of unilateral nephrectomy in mice. The latter probably reflects synthesis of new cell membrane.

Three papers in the current symposium add to our knowledge concerning the biochemistry of CRG. Ouellette discusses the possibility that analysis of renal mRNA during renal growth has not been sufficiently thorough. The mRNA's that regulate gene expression and growth may not be required at abundant levels; thus, they might not be detected by methods used in previous studies. Accordingly, he feels that other methodology must be developed and utilized. It is his opinion that recombinant DNA technology to investigate genetic regulation during compensatory hypertrophy is certain to define renal growth at the molecular level.

Austin et al in this symposium present data indicating that polyamine metabolism may play an important role in CRG. Their work underscores the rapid inducibility of ornithine decarboxylase, the rate-limiting enzyme for polyamine biosynthesis. Further, their findings with an in vitro assay using ornithine decarboxylase activity as a growth index support the existence of a circulating renal growth regulator secondary to unilateral nephrectomy.

Bergeron and Hoang examine the role of adenosine and adenosine deaminase in CRG. When complete inhibition of adenosine deaminase was achieved by injecting coformycin, a specific adenosine deaminase inhibitor, renal adenosine increased and CRG took place. The authors postulate from their in vivo and in vitro studies that CRG could be due to the intracellular action of adenosine acting as a secondary messenger for cell proliferation.

Two papers concerned with physiological aspects of CRG are included. The paper written by Zelman, Zenser, and Davis deals with CRG following unilateral renal obstruction. The authors point out that both the obstructed and contralateral kidneys grow. In the kidney undergoing obstruction, renal mass increases over 7 to 10 days, followed by a progressive decline in

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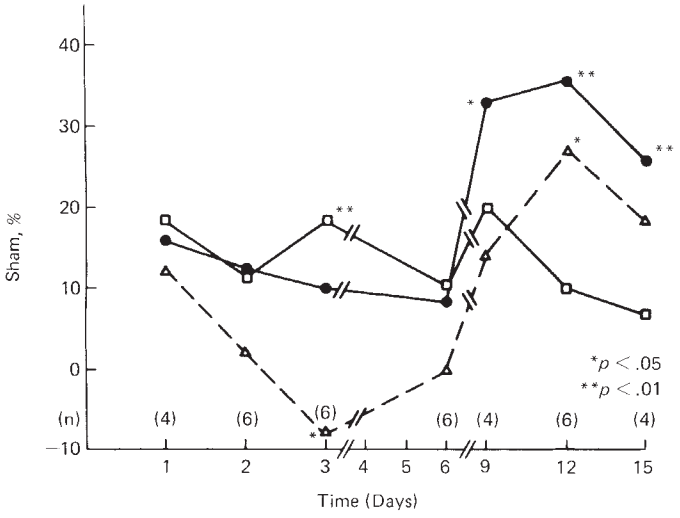

Fig. 1. *Changes in RNA and DNA following unilateral nephrectomy versus sham operation.* Results are expressed as a percentage increase relative to concurrent sham. Symbols are: ●, total RNA; △, total DNA; □, RNA/DNA; *, $P < 0.05$; **, $P < 0.01$. The figure was taken from work of Austin et al reported in this symposium, but it has not been published with the manuscript.

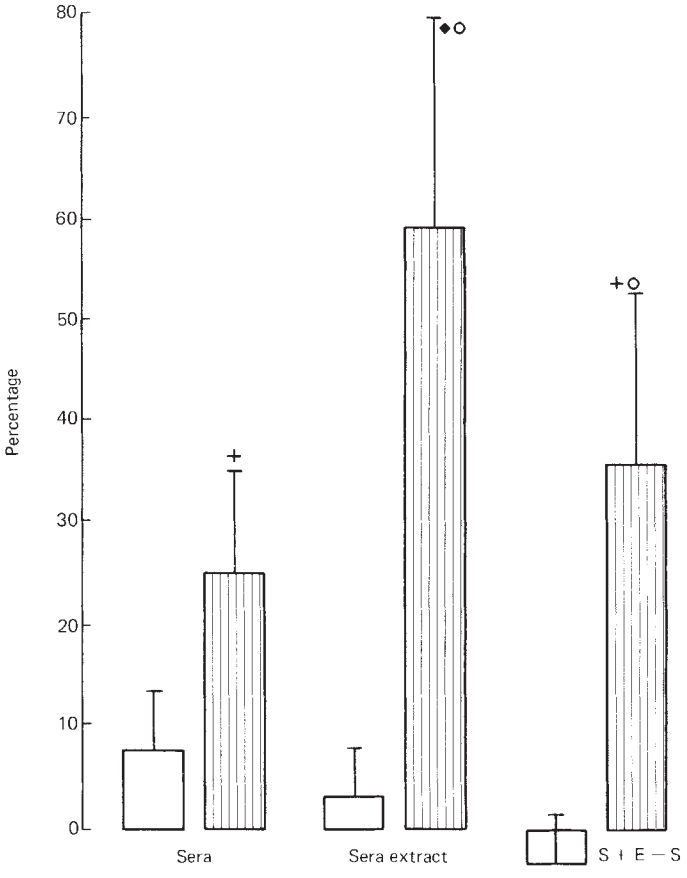

Fig. 2. *Percentage of change in incubating rat kidney fragments induced by adding sera and/or extracts from young and old rats 20 hr after unilateral nephrectomy or sham operation.* The average ± SEM of six rats is shown. Symbols are: □, old breeder rats (426 g ± 29 SEM); ▥, younger rats (241 ± 12 SEM); +, $P < 0.05$; ◆, $P < 0.01$, compared to fragments incubating in neither sera nor extracts (pair analysis); ○, $P < 0.05$ compared to products from old rats (group analysis).

mass. Growth is more obvious in younger than in older animals. They suggest that growth of the obstructive kidney, due largely to proliferation of interstitial fiberblasts and macrophages, may be a local response to injury. Fibroblasts, cultured from the medulla of the obstructive kidney, show an increased growth response. In contrast, the contralateral kidney enlarges as a result of hyperplasia and hypertrophy of the renal parenchyma with the onset of the growth process delayed relative to the obstructive kidney. The differential growth characteristics of the two kidneys in this model make this an interesting investigative tool for future studies on hypertrophy and hyperplasia.

Hayslett's paper stresses a point noted by Zelman, Zenser and Davis, that is, CRG is not as great in older animals compared to younger ones. This should not surprise clinicians who have observed the superior renal regeneration and recovery in their younger patients following acute renal failure. Precise reasons for the relatively poor growth in older kidneys are unknown. The previously described renotropic factor and the tissue response to it could be involved. Since a kidney extract and a serum factor that could incite and regulate renal growth have been described in rats, my laboratory compared both factors in young and old rats after unilateral nephrectomy in preliminary studies (Fig. 2). The factors obtained from older rats weighing an average of 426 g were compared to those of younger rats, weighing an average of 241 g. Twenty hours after uninephrectomy, sera removed from the young unilaterally nephrectomized rats significantly increased thymidine incorporation into DNA of incubating rat renal slices (23%). In contrast, sera obtained from the old breeder rats stimulated incorporation only 7%, an average that was not significantly different from control. When both sera and extracts were taken from these two different age groups of rats, the combination from young rats stimulated thymidine incorporation into DNA nearly 60% and was elevated significantly above control, whereas products from older rats failed to stimulate isotope incorporation. The last set of bars in Figure 2 shows that when the stimulatory factors in sera were excluded, extracts from the younger rats still significantly enhanced thymidine incorporation into DNA. Accordingly, it would appear that both sera and tissue activators from younger rats can enhance certain aspects of renal growth in contrast to products obtained from older rats.

Renotropic factor(s)

In the 6 years since the previous symposium on compensatory renal growth [2, 3] the greatest gains have probably been made in ascertaining the presence of a specific substance, renotropin, that stimulates renal growth. The possibility that a specific circulating renal growth factor exists is strengthened by the finding of specific mitogenic stimulators of growth for other organs. Patt and Houck emphasize in their paper that the three principal forms of growth, that is embryonic growth, wound-repair compensatory hypertrophy, and neoplastic growth, are capable of being stimulated through circulating humoral factors. They discuss the more commonly accepted specific organ

stimulators such as epidermal growth factor, fibroblast growth factor, and so forth.

Malt summarized pros and cons for the existence of renotropin, by discussing the evidence behind the theory that regulators of CRG are probably humoral. It is his opinion that the best evidence for renotropin's existence can be derived from parabiotic studies. He points out that once compensatory hypertrophy takes place, separation of the rat pairs returns kidney mass toward baseline, suggesting that renotropin must be present to maintain hypertrophy.

While Dr. Malt reviews many of the shortcomings of different experimental designs, the positive results from different laboratories [8] using multiple techniques and indices of growth make the existence of renotropin highly likely despite these problems.

In their studies, Harris, Hise, and Best investigated a renotropic factor in urine. Because the kidney is responsible for diverse functions — excretory, metabolic, and humoral — these authors propose that reduction of one or a combination of these functions probably signals CRG. In this study, they use a previously described half-urine reinfusion technique [9]. Their earlier studies had demonstrated that reinfusion of urine over 24 hr increases renal protein synthesis. In their present study, they show that reinfusion, even over 3 hr, can increase thymidine incorporation into DNA and choline incorporation into phospholipids. In addition, adding urine directly to incubating renal fragments stimulates growth. The urinary growth factor that is retained in dialyzed urine and is not deactivated by boiling has a molecular weight of greater than 10,000. The preceding observation duplicates those found for the serum factor [8] (Gaydos, Goldin, Jenson, Gersten, Boedecker, Bartz, and Preuss, submitted for publication). Again, like the serum factor, adding more urine causes a finite increase in the growth which cannot be increased further [10]. As a final similarity, the growth factor is not produced by kidneys since removal of one kidney did not enhance the urine effect [8]. The comparisons suggest that the urine and serum factors may be the same, at least in part. Harris and Best postulate that removal of renal mass decreases excretion of the growth factor and raises its circulatory concentration, which incites renal growth.

Only a few laboratories have been able to show the presence of renotropin through in vitro assay [8]. Amplification of the growth indices of in vitro assays is essential because the small stimulation hinders extensive investigations concerning the physiology and biochemistry of renotropin. Yamamoto, Kanetake, and Yamada have developed an economical tissue culture system in which they synchronize cell growth to maximize the renotropic stimulation in serum from unilaterally nephrectomized rabbits. Using their methodology, they show a maximal stimulation from serum 7 to 10 days after uninephrectomy; the magnitude of stimulation was three- to fourfold above baseline. This assay system with its higher degree of amplification may represent a significant breakthrough which will allow more extensive studies and purification of the factor.

Other aspects of CRG phenomena

The final section of this symposium examines the association between CRG and hypertension — diabetes mellitus. Because many of his experimental models caused both CRG and hypertension, Braun Menendez, to whom the symposium is dedicated, postulated that renotropin not only initiates and/or regulates renal growth, but is the basis for some forms of hypertension. According to his hypothesis, hypertension develops when the concentrations of renotropin rise secondary to the loss of renal mass. Other studies support the viability of this theory. Greenwood, Nassim, and Taylor [11] noted that normal kidneys had to be removed to maintain Goldblatt hypertension. They proposed that the normal kidney either excretes or destroys the renal pressor substance. Later, Fregley and Field [12] noted a correlation between kidney size and hypertension, that is, the greater the kidney weight, the higher the blood pressure. Furthermore, Japanese investigators have shown that unilateral nephrectomy causes an even greater elevation in blood pressure of the spontaneously hypertensive rat (SHR) [13].

Braun Menendez felt that the weakest link in his hypothesis was that no definitive proof was available for the existence of renotropin [14, 15]. Obviously, his hypothesis was proposed prior to the development of the various assays for renotropin [8]. Preuss and Goldin follow renotropic activity in the sera of SHR rats. Rats between 6 and 16 weeks of age, with untouched kidneys, showed a relatively enhanced renotropic activity in their sera when compared to normotensive rats. Other aspects of the CRG system seemed to be normal. They postulated that to maintain normal renal size, these rats may require a higher level of circulating renotropin. This, in return influences blood pressure regulation in some manner. This study deserves further investigation in light of Braun Menendez's early postulate [14, 15].

Renal growth during diabetes has long interested many investigators. Renal mass and glomerular filtration rate are increased in the kidneys of young insulin-dependent diabetic patients. In his investigation with experimentally induced diabetes mellitus in rats, Seyer-Hansen corroborates that diabetes mellitus increases renal weight and gomerular filtration rate. This CRG is similar biochemically and physiologically to that following unilateral nephrectomy, but could not be secondary to the mechanism proposed in the symposium paper by Harris, Hise, and Best since GFR is augmented in the face of growth. Further, combined diabetes mellitus and unilateral nephrectomy can augment renal growth even greater than with one state alone. Seyer-Hansen finds a very close association between circulating glucose levels and kidney size. This model of renal growth, which may or may not be different from that seen following unilateral nephrectomy, is interesting because the pathogenesis of diabetic nephropathy may relate to CRG [16]. As a final point, the development of CRG in diabetes mellitus suggests that glucose, glucagon, and/or insulin could be involved in CRG.

While the importance of renotropin has been studied extensively in rats and rabbits, it is comforting to find a renotropic factor present in humans. The work of Yamada et al shows the existence of a human renal growth factor in sera from unilaterally nephrectomized patients. Six of the sera were derived from renal cancer-bearing patients and two from renal transplant donors.

Knowledge concerning CRG and its various effects has grown slowly over the years. Since the last major symposium on the subject [2, 3], many investigators have searched for a renotropic agent. Its existence has been suggested by evidence gathered from many laboratories using multiple different techniques and indices of growth. Whether this agent is a common,

established hormone with more apparent functions or one not yet identified and named is unknown. If it plays a role in hypertension and/or is responsible for diabetic renal growth and nephropathy remains to be established. Findings of Shames, Corriere, and Berkowitz [17] suggest that CRG influences renal sodium handling, and Garcia-Caceres and Ortega [18] hypothesize that CRG could play a role in pathogenesis of certain renal diseases. Accordingly, it is hoped that this symposium will provide impetus for further investigations along these lines. When future symposia are held, we may have clearer knowledge of the factors controlling CRG and their relation to other states.

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Note added in proof

The reference cited as submitted for publication in the *Renotropic factor(s)* section by GAYDOS DS, GOLDIN H, JENSON B, GERSTEN D, BOEDECKER B, BARTZ C, and PREUSS HG has recently been accepted in *Renal Physiology* with the title, "Partial characterization of a renotropic factor."